REMARKS

Claims 8 and 9 have been cancelled without prejudice.

Claims 1, 4, and 5 have been amended to recite "wherein the mevalonate operon comprises polynucleotides that encode MvaA (hydroxymethylglutaryl-CoA reductase), Idi (isopentenyl diphosphate isomerase), Hcs (hydroxymethylglutaryl-CoA synthase), Mvk (mevalonate kinase), Pmk (phosphomevalonate kinase), and Mvd (diphosphomevalonate decarboxylase)." Support for this amendment is found in the specification at, for example, page 5, lines 12-24. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l) (8th ed. Rev. 5, August 2006, pp. 600-92 and 600-84).

Claims 1 and 4 have also been amended to recite the term "coenzyme Q-10 (CoQ10)." This amendment is for clarification purposes only and does not change the scope of the claims in any way.

The specification has also been amended to present an Abstract on a separate sheet as required by 37 CFR § 1.72(b). Support for this amendment is found, for example, in the underlying International Application Number PCT/EP04/07025 (front page).

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

Objections:

The Examiner objected to the abstract "because the abstract should be on a separate sheet of paper." (Paper No. 20061031 at 2).

We note that the underlying International Application Number PCT/EP04/07025 contained an Abstract on the front page. For the convenience of the Examiner and to further prosecution, the specification has been amended to present an Abstract on a separate sheet as required by 37 CFR § 1.72(b). Accordingly, withdrawal of the objection is respectfully requested.

The Examiner also provisionally objected to claims 1 and 9. (Paper No. 20061031 at 2-3). The Examiner asserted that "should claim 1 be found allowable, claim 9 will be objected to ... as being a substantial duplicate thereof." (*Id.* at 2).

With a view towards furthering prosecution, claim 9 has been cancelled, without prejudice. In view of these amendments, it is believed that the provisional objection of claims 1 and 9 is rendered moot. Accordingly, withdrawal of the objection is respectfully requested.

The Examiner also objected to claims 1, 2, 4, and 9. (*Id.* at 3). The Examiner asserted that "[c]laims 1, 2, 4 and 9 use[ ] [the] abbreviation CoQ10 in the claims," and the Examiner "suggest[ed] expanding the abbreviation to recite the full form of what the abbreviation stands for at least in the first recitation of the abbreviation." (*Id.*).

As suggested by the Examiner, and with a view towards furthering prosecution, claims 1, 2, and 4 have been amended to recite "coenzyme Q-10 (CoQ10)." In view of these amendments, it is believed that the objection is rendered moot. Accordingly, withdrawal of the objection is respectfully requested.

§112, First Paragraph Rejections:

1. Written Description

Claims 1-7 and 9 have been rejected under 35 U.S.C. §112, first paragraph. (Paper No. 20061031 at 3). In making the rejection, the Examiner asserted that claims 1-7 and 9 "contain[] subject matter, which was not described in specification ...." (*Id.*). The Examiner further asserted that "[n]o information, beyond the characterization of a plasmid pBR-K-mev-op-R114 ... has been provided by the applicants." (*Id.*). The Examiner also asserted that "the claims are directed to a process for CoQ10 production by a modified bacterium of genus *Rhodobacter*, wherein the bacterium has been modified by introducing a mevalonate operon from a microorganism belonging to the genus of *Paracoccus* ... with no support in the specification for the structural details associated with the function i.e., mevalonate operon activity, encoding polynucleotide isolated from genus *Paracoccus*." (*Id.* at 3-4). The Examiner then concluded that "one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed." (*Id.* at 4).

With a view towards furthering prosecution, independent claims 1, 4, and 5 have been amended to recite a process "wherein the mevalonate operon comprises polynucleotides that encode MvaA (hydroxymethylglutaryl-CoA reductase), Idi (isopentenyl diphosphate isomerase), Hcs (hydroxymethylglutaryl-CoA synthase), Mvk (mevalonate kinase), Pmk (phosphomevalonate kinase), and Mvd (diphosphomevalonate decarboxylase)." And, claim 9 has been cancelled.

As amended, claims 1, 4, and 5 recite ***specific structural polynucleotides coding for specific enzymes***, namely MvaA (hydroxymethylglutaryl-CoA reductase), Idi (isopentenyl diphosphate isomerase), Hcs (hydroxymethylglutaryl-CoA synthase), Mvk (mevalonate kinase), Pmk (phosphomevalonate kinase), and Mvd (diphosphomevalonate decarboxylase). Claims 1, 4, and 5, as amended, are also specifically tied to a recited function, namely CoQ10 production. Support for these amendments is found virtually *in haec verba* in the specification. (*See, e.g.*, Specification at page 5, lines 12-24 and in the Example). Accordingly, the polynucleotides sequences recited in the independent claims are specifically tied to structure and function. Thus, there is a built-in tie between the recited microorganisms, which are engineered to contain specific polynucleotides that encode ***specific*** enzymes and the claimed functional outcome, namely "CoQ10 production." Moreover, the specification exemplifies ways to obtain the microorganisms in the currently claimed process. (*See, e.g.*, pages 7-12 in the Example and Figure 1). Nothing more need be provided. Thus, in view of these amendments, it is respectfully submitted that the claims fully satisfy the written description requirement.

In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot and should be withdrawn.

2. Enablement

Claims 1-7 and 9 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. (Paper No. 20061031 at 5). In making the rejection, the Examiner acknowledged that the specification is "enabling for a process for CoQ10 production comprising introducing a plasmid pBR-K-mev-op-R114 comprising a

mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens* of strain ATCC 21588 into a microorganism belonging to the *Rhodobacter sphaeroides* and said modified microorganism, ..." (*Id.*).

The Examiner, however, asserted that the specification "does not reasonably provide enablement for a process for CoQ10 production comprising introducing any mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter* and said modified microorganism." (*Id.*).

Initially, we note it is the Examiner's burden to demonstrate that a specification is not sufficiently enabling. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). To carry his/her burden, the Examiner must identify and clearly articulate the factual bases and supporting evidence that allegedly establish that undue experimentation would be required to carry out the claimed invention. *Id.* at 370. It is well established that claims must be separately analyzed. *Ex parte Jochim*, 11 USPQ2d 561 (BPAI 1988).

As amended, claims 1, 4, and 5 recite ***specific structural polynucleotides coding for specific enzymes***, namely MvaA (hydroxymethylglutaryl-CoA reductase), Idi (isopentenyl diphosphate isomerase), Hcs (hydroxymethylglutaryl-CoA synthase), Mvk (mevalonate kinase), Pmk (phosphomevalonate kinase), and Mvd (diphosphomevalonate decarboxylase). The process recited in claims 1, 4, and 5 is also specifically tied to a recited function, namely CoQ10 production. Accordingly, the engineered microorganisms recited in the independent claims process are specifically tied to structure and function. Thus, there is a built-in tie between the recited

microorganisms, which are engineered to encode ***specific*** enzymes and have a specific function i.e., CoQ10 production. Moreover, the specification exemplifies ways to obtain the microorganisms utilized in the currently claimed process. (*See, e.g.*, pages 7-12 in the Example and Figure 1). With these amendments, it is respectfully submitted that the Examiner's concerns regarding the scope of the independent claims, *i.e.*, "***any mevalonate operon*** of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter*," is rendered moot. (Paper No. 20061031 at 5) (emphasis added).

Moreover, as is well accepted, even a "considerable amount" of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance. MPEP § 2164.05 and *In re Wands*, 8 USPQ at 1404. In addition, "a patent need not teach, and preferably omits, what is well known in the art." MPEP § 2164.01 (8th ed. Rev. 5, August 2006, p. 2100-187) *citing In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In this regard, we note that the specification provides ample disclosure sufficient to inform a skilled artisan that the Applicants enabled the currently claimed process and microorganisms for CoQ10 production. For example, the specification discloses a detailed example and a detailed Figure 1 that provide sufficient instruction to one skilled in the art on how to make and use the currently claimed process for CoQ10 production comprising ***specific*** microorganisms coding for ***specific*** enzymes.

Specifically, the specification discloses, *inter alia*, how to obtain and use a process for CoQ10 production comprising introducing a plasmid pBBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens* of strain ATCC 21588 into a microorganism belonging to *Rhodobacter sphaeroides*. Thus, the specification discloses how to obtain and use the microorganisms according to the process of the present invention. (*See, e.g.*, pages 7-12 in the Example and Figure 1). Thus, identifying the microorganisms capable of producing CoQ10 according to the amended process claims is a matter of applying the disclosure in the specification of how to make such microorganisms and testing the CoQ10 productions of the microorganisms compared to the unmodified microorganisms. (*See* Table 3). It is respectfully submitted that such activity is not undue experimentation.

For the reasons set forth above, it is respectfully submitted that the rejection has been rendered moot and should be withdrawn.

Rejection Under 35 USC § 103:

Claims 1-7 and 9 were rejected under 35 USC § 103 as being unpatentable over Berry *et al.*, WO 02/099095 ("Berry") in view of Hahn *et al.*, WO 02/10398 ("Hahn"), Gokarn *et al.*, U.S. Patent Publication No. 2003/0219798 ("Gokarn"), and Yoshida *et al.*, "*Production of Ubiquinone-10 Using Bacteria*," Journal of General and Applied Microbiology, vol. 44, no. 1, pp. 19-26 (1998) ("Yoshida"). (Paper No. 20061031 at 9-11).

The rejection respectfully is traversed.

Berry discloses "[i]solated polynucleotides encoding polypeptides having the activity of enzymes in the mevalonate pathway, *e.g.* hydroxymethylglutaryl-CoA

reductase, isopetenyl diphosphate isomerase, hydroxymethylglutaryl-CoA synthase, mevolante kinase, phosphomevalonate kinase, or diphosphomevalonate decarboxylase." (Abstract). Berry further discloses that these enzymes are "useful for recombinantly producing . . . carotenoids like phytoene, lycopene, β-carotene, zeaxanthin, canthaxanthin astaxanthin, adonixanthin, cryptoxanthin echinenone and adonirubin." (*Id.*).

Hahn discloses "specific genes of the mevalonate and isoprenoid biosynthetic pathways, and of inactive gene sites (the pseudogene) to (1) enhance biosynthesis of isopentenyl diphosphate, dimethylallyl diphosphate and isoprenoid pathway derived products in the plastids of ***transgenic plants and microalagae*** (2) create novel antibiotic resistant transgenic plants and microalgae and (3) create a novel selection system and/or targeting sites for mediating the insertion of genetic material into plant and microalgae plastids." (Abstract). Hahn further discloses that "[t]he specific polynucleotides to be used, solely or in any combination thereof, are publicly available from GeneBank and contain open reading frames having sequences that upon expression will produce active proteins with the following enzyme activities: (a) acetoacetyl CoA thiolase (EC 2.3.1.9), (b) 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthase (EC 4.1.3.5), (c) HMG-CoA reductase (EC 1.1.1.34), (d) mevalonate kinase (EC 2.7.1.36), (e) phosphomevalonate kinase (EC 2.7.4.2), (f) mevalonate diphosphate decarboxylase (EC 4.1.1.33), (g) isopentenyl diphosphate (IPP) isomerase (EC 5.3.3.2), and (b) phytoene synthase (EC 2.5.1.32)." (*Id.*).

Gokarn discloses "isolated nucleic acids, substantially pure polypeptides, host cells, and methods and materials for producing various isoprenoid compounds." (Abstract).

Yoshida discloses "three strains, *Agrobacterium tumefaciens* KY-3085 (ATCC4452), *Paracoccus denitrificans* KY-3940 (ATCC19367) and *Rhodobacter sphaeroides* KY-4113 (FERM-P4675)" as "excellent producers" of CoQ10. (Abstract and page 19). ***Such strains were obtained by random mutagenesis and selection.*** (Pages 20-24).

In making the rejection, the Examiner asserted that Berry discloses "the sequence of plasmid pBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of Paracoccus zeaxanthinifaciens of strain ATCC 21588 (plasmid containing the first 4 genes of the mevalonate operon as described in detail in Example 6 of WO 02/099095 and isolated by PCR amplification by using PCR primer *hcs*-5326 with SEQ ID NO: 1 and a PCR primer *mvd*-9000 with SEQ ID NO: 2 that flanks SEQ ID NOS : 46 to 52 of WO 02/099095, having a mutation in *mvk* gene, resulting in a change of amino acid residue 265 from alanine to valine; A265V as compared to the wild-type mevalonate operon sequence)." (Paper No. 20061031 at 9).

The Examiner asserted that Hahn discloses "methods of manipulation of the mevalonate and isoprenoid pathways to create novel traits in organisms of interest for the production of isoprenoids (CoQ10)." (*Id.* at 10).

The Examiner asserted that Gokarn discloses "the identification of polynucleotide sequences involved in the isoprenoid production and also use of *Rhodobacter sp.* microorganism for the production of CoQ10 by introducing

heterologous genes involved in the isoprenoid production (CoQ10) in said microorganism (Paragraphs 0028-0033, 0137-0147 and 0157-0163 and claims 75-102)." (*Id.*).

The Examiner then asserted that Yoshida discloses "*Rhodobacter sphaeroides* as an excellent producer and host for the production of ubiquinone-10 (CoQ10) an isoprenoid compound (Abstract and Introduction section, page 19)." (*Id.*).

The Examiner then contended that "[t]he above mentioned references teach all the elements of the instant application and combining the teachings of the above references it would have been obvious to one of ordinary skill in the art at the time of the instant invention to generate a bacterium that can be used for a process in the production CoQ10 and such a bacterium and said process would comprise introducing a mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter*." (*Id.* at 11).

With a view towards furthering prosecution, however, independent claims 1, 4, and 5 have been amended to recite a process "wherein the mevalonate operon comprises polynucleotides that encode ***MvaA (hydroxymethylglutaryl-CoA reductase), Idi (isopentenyl diphosphate isomerase), Hcs (hydroxymethylglutaryl-CoA synthase), Mvk (mevalonate kinase), Pmk (phosphomevalonate kinase), and Mvd (diphosphomevalonate decarboxylase)***." And, claim 9 has been cancelled.

It is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ

785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO must include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). The factual inquiry whether to combine documents must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to combine "***must be based on objective evidence of record***." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002).

The rejection is devoid of *any* evidence - or even argument - in support of the proposed combination. All that is there is a conclusory statement that "[t]he above mentioned references teach all the elements of the instant application and combining the teachings of the above references it would have been obvious to one of ordinary skill in the art." (Paper No. 20061031 at 11). What the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Berry using Hahn, Gokarn, and Yoshida to arrive at the claimed method. As is well settled, an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done. *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). But this is precisely what the Examiner has done here. Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

Notwithstanding the legally insufficient nature of the rejection, we note that the rejection is also factually insufficient to support a rejection under § 103(a). In doing so we observe that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, ***all claim limitations must be taught or suggested by the prior art***." MPEP § 2143.03 (citing *In re Royka*, 180 USPQ 580 (CCPA 1974)) (emphasis added).

Assuming *arguendo* that Berry is properly combinable with Hahn, Gokarn, and Yoshida, which it is not, such a combination does not produce the process of the amended claims. Berry discloses the over expression of the ***endogenous*** mevalonate pathway whereas the presently claimed process relates to the ***heterologous*** expression of the mevalonate pathway from the genus *Paracoccus* in the genus *Rhodobacter*. Here, the claimed process has nothing to do with the ***endogenous*** mevalonate pathway that is disclosed in Berry. Furthermore, Berry is concerned with the enhanced production of carotenoid compounds. Berry discloses that over expression of the ***endogenous*** mevalonate operon results in enhanced production of carotenoids and their precursors ***NOT*** the overproduction of coenzyme Q10 as claimed. Thus, the rejection does not - and cannot - identify where in Berry there is disclosed the use of heterologous sequences in a host microorganism as claimed.

It is respectfully submitted that Berry does not disclose or suggest the currently amended claims. Unfortunately for the Examiner, neither Hahn, nor Gokarn,

nor Yoshida fill the factual gap left by Berry. Hahn discloses the heterologous expression of the mevalonate pathway described in plastids of plants and micro algae ***NOT*** in bacteria, such as *R. sphaeroides*. Moreover, the technology required to manipulate plant and microalgae genes is not the same as that required to manipulate bacterial genes. Thus, Hahn is non-analogous and is not properly citeable. CITE

Also, in Hahn, the aim is not the production of an isoprenoid compound, such as coenzyme Q10, but to create antibiotic resistant transgenic plants and microalgae and to provide a selection system for transgenic plants and microalgae. Thus, Hahn discloses that introducing the mevalonate pathway into plastids of plants and microalgae allows one to use inhibitors of the endogenous, non-mevalonate pathway, as selective agents to differentiate cells with transgenic plastids from native cells, which is not even close to the process for coenzyme Q10 production as recited in the amended claims.

Yoshida, on the other hand, describes the production of coenzyme Q10 by three specific bacterial strains (*Agrobacterium tumefaciens KY-3085* (ATCC4452), *Paracoccus denitrificans* KY-3940 (ATCC19367) and *Rhodobacter sphaeroides* KY-4113 (FERM-P4675)). These three strains are part of strain collection from the company Kyowa Hakko Kogyo Co, Ltd, and all three described strains were obtained by ***random mutagenesis and selection*** for higher coenzyme Q10 production using a treatment with N-methyl-N'-nitro-N-nitrosoguanidine. Yoshida discloses that that these selected strains were largely improved in their capacity to produce coenzyme Q10 compared to the wild type strains. Therefore, at best, Yoshida teaches that *A. tumefaciens, P.* denitrificans and *R. sphaeroides* could be "excellent producers of coenzyme Q-1" if one could improve their production by ***random mutagenesis and selection***.

At bottom, one would not look to Yoshida for ideas/methods to use in engineering a bacterial strain as is presently claimed. Thus, Yoshida is also non-analogous art and can not be cited. MPEP § 2141.01(a) (8th ed. Rev. 5, August 2006, p. 2100-119). Thus, none of the Examiner's secondary references fill the gaps left by Berry.

Thus, the proposed combination falls short of disclosing or suggesting the currently claimed process. In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Accordingly, for the reasons set forth above, entry of the amendments, withdrawal of the objections and rejections, and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on April 27, 2007.

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